Primary Dystonia Etiology

It is suspected to be caused by a pathology of the central nervous system, likely originating in those parts of the brain concerned with motor function, such as the basal ganglia, and the GABA (gamma-aminobutyric acid) producing Purkinje neurons. The precise cause of primary dystonia is unknown. In many cases it may involve some genetic predisposition towards the disorder combined with environmental conditions.

Wirth et al. applied whole-exome sequencing to DNA samples from 32 patients with early-onset or familial dystonia investigated by sequencing of a 127 movement disorders-associated gene panel. Dystonia was described according to the familial history, body distribution, evolution pattern, age of onset, associated symptoms and associated movement disorders. Rate of diagnoses was evaluated for each clinical feature.

They identified causative variants for 11 patients from 9 families in CTNNB1, SUCLG1, NUS1, CNTNAP1, KCNB1, RELN, GNAO1, HIBCH, ADCK3 genes, yielding an overall diagnostic rate of 34.4%. Diagnostic yield was higher in complex dystonia compared to non-complex dystonia (66.7%-5.9%; $p < 0.002$), especially in patients showing intellectual disability compared to the patients without intellectual disability (87.5%-16.7%; $p < 0.002$).

This approach suggests WES as an efficient tool to improve the diagnostic yield after gene panel sequencing in dystonia. Larger study are warranted to confirm a potential genetic overlap between neurodevelopmental diseases and dystonia [1)].

The majority of early-onset primary dystonias, which may appear during childhood or early adulthood, are due to mutations of a gene known as DYT1. This gene has been mapped to the long arm of chromosome 9 at 9q34.1. In about 90 to 95 percent of cases, symptoms begin in a limb and then spread to other regions of the body. This form of dystonia has an average age of onset of 12 and seldom develops after age 29.

DYT6 dystonia is an autosomal dominant primary dystonia that has been mapped to chromosome 8 (8p21q22). It is rarer than DYT1 dystonia and has been studied in two Mennonite families in the United States. In nearly all individuals with this form of dystonia, the disorder begins at an initial site but spreads to multiple body regions, most commonly the limbs, head, or neck. Severe difficulties with speech articulation have been noted.

Other familial primary dystonias identified are DYT7, DYT2, and DYT4, all of which have been noted in specific ethnic groups, primarily of European descent.

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Wirth T, Tranchant C, Drouot N, Keren B, Mignot C, Cif L, Lefaucheur R, Lion-François L, Méneret A, Gras D, Roze E, Laroche C, Burbaud P, Bannier S, Lagha-Boukbiza O, Spitz MA, Laugel V, Bereau M, Ollivier E, Nitschke P, Doummar D, Rudolf G, Anheim M, Chelly J. Increased diagnostic yield in complex dystonia through exome sequencing. Parkinsonism Relat Disord. 2020 Apr 20;74:50-56. doi: 10.1016/j.parkreldis.2020.04.003. [Epub ahead of print] PubMed PMID: 32334381.